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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,177	03/19/2004	Gregory M. Landes	21402-665 (CURA 965)	8179

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,177	LANDES ET AL.	
	Examiner	Art Unit	
	MEERA NATARAJAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,33 and 34* is/are pending in the application.

4a) Of the above claim(s) *13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-12, 23-30, 33, 34* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments to the claims in the reply filed on 03/08/2010 is acknowledged and entered into the record.

2. Claims 1-30, 33 and 34 are pending. Claims 13-22 have been withdrawn as being directed to non-elected inventions.

3. Claims 1-12, 23-30, 33, and 34 will be examined on the merits.

Claim Rejections Maintained - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. The rejection of Claims 1, 4-10, and 12 under 35 U.S.C. 102(e) as being anticipated by McIntire et al. (PgPub 20030124114) is maintained for the reasons of record.

6. The claims are drawn to an isolated human antibody or binding fragment thereof that specifically binds to human T cell, immunoglobulin domain and mucin domain 1 (TIM-1), wherein said antibody or antigen-binding fragment thereof specifically binds an epitope comprising SEQ ID NO: 87 and wherein said antibody is conjugated to a therapeutic agent and a hybridoma cell line producing said antibody.

7. McIntire et al. teach T cell regulatory genes and there association with immune dysfunction. McIntire et al. disclose polymorphisms of TIM proteins including TIM-1, TIM-3 and TIM-4. McIntire et al. disclose binding agents, including nucleic acids and antibodies for functional studies such as diagnostics for assessing tumor resistance to cancer therapy. McIntire et al. disclose TIM blocking agents find use as therapeutics in the treatment of immune dysfunction and disorders of cell survival, including malignancies (see paragraph [0009]). McIntire et al. disclose the production of antibodies using hybridomas as well as genetic engineering. McIntire et al. disclose chimeric antibodies made through recombinant means in order to produce an antibody with human domains and the production of humanized antibodies (see paragraphs [0073-85]). McIntire et al. further disclose conjugated antibodies and antibody fragments. McInitre et al. disclose SEQ ID NO:87 of the instant application and therefore teach an isolated human antibody that specifically binds to a polypeptide comprising said sequence (see attached sequence alignment).

Response to Arguments

8. Applicants argue McIntire et al. does not teach or suggest any epitopes on the TIM-1 antigen, nor is there any disclosure regarding antibodies that specifically bind to a particular epitope on TIM-1. Thus, the McIntire reference does not teach any epitopes of TIM-1, let alone the particular epitope recited by amended claim 1 and its dependent claims. This argument has been carefully considered but not found persuasive.

9. Applicants are correct in pointing out that McIntire et al. is silent in regards to the specific epitope of TIM-1 recited in Claim 1 (SEQ ID NO:87), however McIntire et al.

disclose polyclonal antibodies directed to the full length TIM-1. It is an inherent property of polyclonal antibodies to contain a mixture of antibodies with different epitopic specificities to the same antigen, and thus a polyclonal antibody directed to TIM-1 would comprise antibodies having an epitope comprising SEQ ID NO:87. Therefore the rejection of record is maintained.

Claim Rejections Maintained - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. The rejection of Claims 1, 4-10, 12 and 23-30 under 35 U.S.C. 103(a) as being unpatentable over McIntire et al. (PgPub 20030124114) in view of Watkins et al. (PgPub 20040162413) is maintained for the reasons of record.

13. The claims are drawn to an isolated human antibody or binding fragment thereof that specifically binds to T cell, immunoglobulin domain and mucin domain 1 (TIM-1),

wherein said antibody is conjugated to a therapeutic agent and a hybridoma cell line producing said antibody and a kit comprising said antibody. Claims 31-33 are drawn to an antibody or binding fragment thereof that specifically binds to the amino acid sequence of SEQ ID NO:87 and an isolated human antibody that binds to TIM-1 and is encoded by a VH3-33 germline with a Kd between 10-7 and 10-14M.

14. The teachings of McIntire are presented in the 102(e) rejection set forth above. McIntire et al. does not teach a kit comprising said TIM-1 antibody or an isolated human antibody encoded by the VH3-33 germline. These deficiencies are made up for by Watkins et al.

15. Watkins et al. teach method of optimizing antibody variable region binding affinity. Watkins et al. teach unvaried human frameworks such as VH3-33 which is used to help eliminate or reduce adverse immune responses when administered therapeutically in most individuals. Watkins et al. also disclose kits comprising a binding molecule (i.e. antibody) and instructions for using said binding molecule to treat a disease in a subject (see paragraph [0038]).

16. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the VH3-33 germline gene disclosed by Watkins et al. to optimize the TIM-1 antibody taught by McIntire et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the teachings of Watkins et al. that optimizing the antibody helps eliminate or reduce adverse immune response effects. In addition it would be obvious to produce a kit comprising the TIM-1 antibody taught by McIntire et al. and instructions

for the treatment of a subject because McIntire et al. disclose the TIM-1 antibody can be used for therapeutic purposes.

Response to Arguments

17. Applicants argue McIntire et al. does not teach or suggest any epitopes on the TIM-1 antigen, nor is there any disclosure regarding antibodies that specifically bind to a particular epitope on TIM-1. Thus, the McIntire reference does not teach any epitopes of TIM-1, let alone the particular epitope recited by amended claim 1 and its dependent claims. This argument has been carefully considered but not found persuasive.

18. Applicants are correct in pointing out that McIntire et al. is silent in regards to the specific epitope of TIM-1 recited in Claim 1 (SEQ ID NO:87), however McIntire et al. disclose polyclonal antibodies directed to the full length TIM-1. It is an inherent property of polyclonal antibodies to contain a mixture of antibodies with different epitopic specificities to the same antigen, and thus a polyclonal antibody directed to TIM-1 would comprise antibodies having an epitope comprising SEQ ID NO:87. Therefore the rejection of record is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 2, 11, 33, 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn to an isolated human antibody or antigen-binding fragment thereof, that specifically binds to human T cell immunoglobulin domain and mucin domain 1 (TIM-1), wherein said antibody or antigen-binding fragment thereof comprises at least 90% identity to specific heavy chain or light chain CDR amino acid sequences.

Written Description Rejection

22. There is insufficient written description encompassing a TIM-1 antibody comprising at least 90% identity to specific CDR or heavy and light chain sequences, because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of TIM-1 are not set forth in the specification as-filed, commensurate in scope with the claimed invention.

23. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

24. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

25. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. Also, the Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

26. Applicant is relying upon certain biological activities and the disclosure of an antibody used in a method for treating renal or ovarian cancer. However, the instant specification does not provide sufficient written description as to the structural features of any antibody which CDRs are 90% homologous to the CDR sequences claimed and the correlation between the chemical structure and the function of the claimed antibody.

27. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths

identify essential sequences for identifying the claimed polypeptide. For example, there is insufficient guidance based on the reliance of a antibody with CDRs that are 90% homologous to the CDR sequences claimed to direct a person of skill in the art to predict particular sequences in which an antibody would still be able to bind in order to perform the disclosed utility of inhibiting cell proliferation in renal and ovarian cancer.

28. Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Based on Lederman's teachings, an antibody which binds to TIM-1, might not bind to a polypeptide which is 90% homologous to the CDRs claimed and therefore not achieve the disclosed use of treating renal and ovarian cancer. In addition, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Amino acid substitutions may affect the immunogenicity of the claimed antibody and there is insufficient guidance in the instant specification as to which amino acids can be substituted and not alter antibody binding or immunogenic capabilities.

29. The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004). The problem here is that the instant specification fails to provide a disclosure of which residues are required for a TIM-1 antibody which is 90%

homologous to be substantially the same and retain the appropriate antibody specificity for an antibody comprising 100% identity with the claimed CDRs (and heavy/light chain). A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

30. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Scope of Enablement Rejection

31. Claim 2, 11, 33, 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human antibody or antigen-binding fragment thereof, that specifically binds to human T cell immunoglobulin domain and mucin domain 1 (TIM-1), wherein said antibody or antigen-binding fragment thereof comprises 100% identity to specific heavy chain or light chain CDR amino acid sequences, does not reasonably provide enablement for wherein said antibody or antigen-binding fragment thereof comprises at least 90% identity to specific heavy chain or light chain CDR amino acid sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

32. The claims are drawn to an antibody comprising heavy and light chain CDRs that are 90% homologous to specific SEQ ID NOs recited in Claims 2, 11 and 34. The claims read on an antibody with alterations in the CDRs.

33. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. J. Mol. Biol. (1996) 262, 732-745, analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733,

right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). Pascalis et al. The Journal of Immunology (2002) 169, 3076-3084 demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (2003) BBRC 307, 198-205, which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Vajdos et al. (2002) 320, 415-428, additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.). Holm et al. (2007) 44, 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen

binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et al. J. Mol. Bio. (1999) 293, 865-881. describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. J. Mol. Biol. (1999) 294, 151-162. state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

34. The references demonstrate that an antibody must not only comprise all 6 CDRs in order to maintain the antigen binding specificity and affinity, but even minor alterations in the CDRs can affect the defined characteristics of the immunoglobulin.

Conclusion

35. Claims 1, 2, 4-12, 23-30, 33 and 34 are rejected.

36. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

37. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Thursday, 9:30AM-7:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

/Larry R. Helms/
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